

# The Association of The Prolongation Of P-Wave Duration With Ascending Aortic Dilatation In Obese Patients

## Obes hastalarda P dalga süresinin uzamasının asendan aort dilatasyonu ile ilişkisi

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### Abstract

**Background:** Ascending aortic dilatation (AAD) is a clinical entity, which is closely related to acute aortic syndromes and can be mortal if not detected at an early stage. Interatrial block (IAB) is a conduction delay between the both atriums and is associated with cardiovascular diseases. We think that IAB may accompany with obese patients with AAD, and the diameter of ascending aorta may be correlated with P-wave duration. Thus, in the current study, we aimed to evaluate the association between AAD and IAB in obese patients.

**Materials and Methods:** A total of 318 consecutive obese subjects who were presented to our outpatient clinic for routine follow-up were enrolled into the study. Standard 12-lead ECGs were recorded. Clinical characteristics, echocardiographic data, and laboratory results of the patients were obtained.

**Results:** The mean age of the patients was  $62.7 \pm 10.3$  years, and 199 (62.5%) of the patients were female. The frequency of IAB was significantly higher and P-wave duration was significantly increased in the AAD (+) patients than in the AAD (-) subjects ( $p < 0.001$  and  $p < 0.001$ , respectively). The strongest correlation was found between ascending aortic diameter and P-wave duration ( $r = 0.713$ ,  $p < 0.001$ ). In linear regression analysis, P-wave duration ( $\beta = 0.695$ ,  $p < 0.001$ ) and left atrial volume index (LAVI) ( $\beta = 0.611$ ,  $p = 0.005$ ) were found to be independent predictors of ascending aortic diameter.

**Conclusions:** We demonstrated that prolongation of P-wave duration and increased LAVI values were significantly associated with ascending aortic diameter. Therefore, we think that P-wave duration may be used in the follow-up of the AAD patients.

**Key Words:** Ascending aortic dilatation, interatrial block, obesity, P-wave duration

### Öz.

**Amaç:** Asendan aort dilatasyonu (AAD), akut aort sendromlarıyla yakından ilişkili olan ve erken bir aşamada tespit edilmezse ölümcül olabilen klinik bir antitedir. İnteratriyal blok (İAB) her iki atriyum arasında bir iletim gecikmesidir ve kardiyovasküler hastalıklar ile ilişkilidir. İAB'nin AAD'li obez hastalara eşlik edebileceğini ve asendan aort çapı ile P-dalga süresinin ilişkili olabileceğini düşündük. Bu nedenle, bu çalışmada obez hastalarda AAD ve İAB arasındaki ilişkiyi değerlendirdik.

**Materyal ve Metod:** Rutin takip için polikliniğimize başvuran 318 ardışık obez hasta çalışmaya dahil edildi. Standart 12 derivasyonlu EKG'ler kaydedildi. Hastaların klinik özellikleri, ekokardiyografik verileri ve laboratuvar sonuçları kaydedildi.

**Bulgular:** Hastaların ortalama yaşı  $62.7 \pm 10.3$  yıl idi ve hastaların 199'u (% 62.5) kadındı. İAB sıklığı ve uzamış P dalga süresi AAD (+) hastalarında AAD (-) gruba göre anlamlı olarak daha yüksekti ( $p < 0.001$  ve  $p < 0.001$ , sırasıyla). En güçlü korelasyon, asendan aort çapı ile P-dalga süresi arasında bulundu ( $r = 0.713$ ,  $p < 0.001$ ). Lineer regresyon analizinde, P-dalga süresi ( $\beta = 0.695$ ,  $p < 0.001$ ) ve sol atriyal volüm indeksi (LAVI) ( $\beta = 0.611$ ,  $p = 0.005$ ) asendan aort çapının bağımsız belirleyicileri olarak bulundu.

**Sonuç:** P-dalga süresinin uzamasının ve artmış LAVI değerlerinin asendan aort çapı ile anlamlı bir ilişkisinin olduğunu gösterdik. Bu nedenle, P dalgası süresinin AAD hastalarının takibinde kullanılabileceğini düşünüyoruz.

**Anahtar kelimeler:** Asendan aort dilatasyonu, interatriyal blok, obezite, P-dalga süresi

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## Introduction

Ascending aortic dilatation (AAD) is a clinical entity, which is closely related to acute aortic syndromes and can be mortal if not detected at an early stage (1). The enlargement of the ascending aorta is defined as aneurysm if it is over the one and a half times the normal diameter. Aortic aneurysm is associated with more than 5% rupture risk per year resulting with death (2). Several local and/or systemic factors have pivotal roles in the pathogenesis of AAD such as increased age, smoking, male gender, familial genetic factors, hemodynamic alterations, inflammation of the aorta, and destructive remodeling of the extracellular matrix (3-7). Recently, several studies have demonstrated that obesity and metabolic syndrome also contribute to dilatation of the aorta (8,9).

Obesity, which is associated with metabolic syndrome and cardiovascular risk factors, has become a major problem threatening public health worldwide (10). Obesity acts on the cardiovascular system directly via inflammatory processes, and indirectly by potentializing comorbid conditions such as diabetes mellitus (DM) and hypertension (HT). As a result, a cardiomyopathy triggered by obesity is occurred. This cardiomyopathy, also known as "obesity cardiomyopathy", has a complex interplay of neuronal, hemodynamic, hormonal, and metabolic factors which contribute to inflammation, hypertrophy, apoptosis, and interstitial myocardial fibrosis (11-14). Increased inflammatory activity and high atrial pressure in obesity cause structural and electrical remodeling of the left atrium (LA). Atrial fibrosis is the underlying mechanism of LA remodeling, which develops atrial fibrillation (AF) in the long term; and its electrocardiographic (ECG) finding is interatrial block (IAB) (15).

IAB, a conduction delay over the Bachmann bundle, is characterized by the presence of a prolonged P-wave duration that exceeds 120 ms on the 12-lead surface ECG (16). IAB is known to be associated with AF, atrial tachyarrhythmias, LA electromechanical dysfunction, thromboembolic ischemic stroke, and increased cardiovascular mortality (17-19). Therefore, IAB may be useful in the follow-up of people with obesity or metabolic syndrome at risk for such clinical scenarios.

Oxidative stress caused by obesity affects the atrial myocardial tissue and leads to IAB, as well as, affects the aortic wall and leads to AAD. We think that IAB may accompany with obese patients with AAD, and the diameter of ascending aorta may be correlated with P-wave duration. Thus, in the current study, we aimed to evaluate the association between AAD and IAB in obese patients.

## Materials and Methods

### Study population

A total of 318 consecutive obese subjects in sinus rhythm who admitted to our outpatient clinic for routine follow-up

between September 2017 and November 2019 were enrolled into this cross-sectional observational study. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m<sup>2</sup>). Obesity was defined as BMI  $\geq 30$  kg/m<sup>2</sup>. Obese subjects were included in the study. The current study consisted of 158 subjects with AAD [AAD (+)], and 160 subjects without AAD [AAD (-)]. AAD was defined as the diameter of ascending aorta  $>40$  mm (20). The exclusion criteria were history of atherosclerotic heart diseases, rheumatic heart disease, bicuspid aortic valve, bundle branch block, left ventricular ejection fraction (LVEF)  $< 55\%$ , chronic liver and kidney insufficiency, evidence of acute infections, chronic autoimmune disease, thyroid and parathyroid dysfunction, uncontrolled hypertension, and poor ECG quality. The study was approved by the local ethics committee (Project No.: 152-05-23, Date: 7/1/2020). Informed consent form was obtained from all patients included in the study.

### Clinical evaluation of the patients

The baseline clinical characteristics of the patients were recorded. Information regarding risk factors, including age, gender, HT, DM, hyperlipidemia (HLP), and smoking status was obtained. Blood samples were drawn by venipuncture to measure complete blood count, routine biochemistry and lipid panel after 12 hours fasting.

### Transthoracic echocardiographic assessment of the patients

The echocardiographic data obtaining was performed in accordance with the American Society of Echocardiography (ASE) criteria (21). All patients underwent 2-dimensional transthoracic echocardiographic (HD11 XE Ultrasound system, Philips, Canada) evaluation. An experienced cardiologist who was blinded to the clinical characteristics of the patients analyzed the all echocardiographic images. The evaluation of aortic root was performed in parasternal long-axis view. AAD was defined as the diameter of ascending aorta  $>40$  mm (20). Left atrial (LA) volume and LVEF were assessed using the modified Simpson biplane method. LA volume was measured from standard apical 4-chamber views at end systole just before mitral valve opening. The left atrial volume index (LAVI) was measured as follows: dividing the LA volume to the body surface area (22).

### ECG analysis of the study population

A standard surface 12-lead ECG (Schiller, Cardiovit AT-10 plus) (filter 150 Hz, 25mm/s, 10mm/mV) was recorded for all patients. ECG images were amplified 8 times and P-wave duration was measured by using semiautomatic digital calipers. The longest p wave duration was recorded in 12-lead surface ECG. The point of initial upward or downward deflection from the isoelectric line was defined as the onset of P-wave. The returning point of the deflection to the initial isoelectric line was defined as the offset of P-wave. P-wave duration longer than 120 msec. without biphasic

morphology in the DII-DIII-aVF leads is determined as partial IAB (p-IAB); and P-wave duration longer than 120 msec. with biphasic morphology in the DII-DIII-aVF leads is determined as advanced IAB (a-IAB) (16). ECG measurements were made by an experienced electrocardiologist who was blinded to the patients' data.

### Statistical analysis

All data were analyzed by using SPSS 25.0 (IBM Corp., Armonk, NY, USA) program. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean  $\pm$  standard deviations and categorical variables were expressed as n and percentages. Continuous variables were compared with Student t test or Mann-Whitney U test according to the distribution. Categorical variables were compared with chi-square and Fisher Exact chi-square tests. Pearson and/or Spearman's correlation coefficient was used for correlation analysis. Receiver operating characteristics (ROC) curve was performed to determine the optimal cut-off value of P-wave duration for predicting AAD. Linear regression analysis was used to determine the independent predictors of diameter of ascending aorta. A p-value  $< 0.05$  was considered as statistically significant.

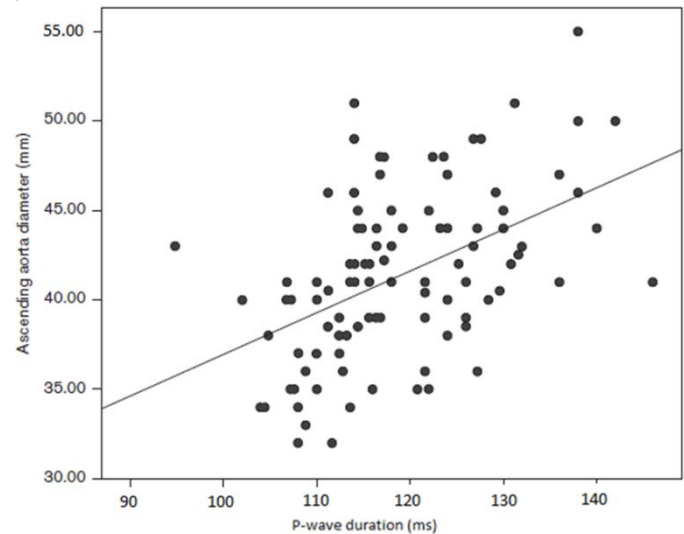
### Results

A total of 318 obese subjects were enrolled into the current study [158 patients in AAD (+) group and 160 patients in AAD (-) group]. The clinical and laboratory characteristics of the patients are presented in the Table-1. The mean age of the patients was  $62.7 \pm 10.3$  years, and 199 (62.5%) of the patients were female. The mean BMI of the patients was  $33.1 \pm 1.5$  kg/m<sup>2</sup>. The frequency of smoking and HT, and mean diastolic BP and the TC level were significantly higher in the AAD (+) group than in the AAD (-) group ( $p = 0.004$ ,  $p = 0.036$ ,  $p = 0.001$  and  $p = 0.017$ , respectively). In present study, AAD (+) group had 77 patients with p-IAB and 25 patients with a-IAB; and AAD (-) group had 35 subjects with p-IAB and 10 subjects with a-IAB. It was found that the frequency of IAB was significantly higher and P-wave duration was significantly increased in the AAD (+) patients than in the AAD (-) subjects ( $p < 0.001$  and  $p < 0.001$ , respectively). However, there were not any significant differences between two groups in terms of age, gender, BMI, heart rate, systolic BP, and history of DM, HLP (Table 1).

In the echocardiographic evaluation, left atrium diameter and LAVI were significantly higher in the AAD (+) group than in the AAD (-) group ( $p = 0.005$  and  $p < 0.001$ , respectively) (Table 2).

In correlation analysis, P-wave duration ( $r = 0.713$ ,  $p < 0.001$ ) (Figure 1) and LAVI ( $r = 0.604$ ,  $p < 0.001$ ) were positively correlated with ascending aortic diameter. In addition, ascending aortic diameter was positively correlated with age, BMI, diastolic BP, and left atrium diameter (Table

3).



**Figure 1.** Correlation between PWD and ascending aortic diameter

**Table 1.** The baseline clinical, electrocardiographic, and laboratory characteristics of study population

	AAD (-) group (n = 160)	AAD (+) group (n = 158)	P Value
Age, years	62.3 $\pm$ 10.2	63.1 $\pm$ 10.5	0.323
Female gender, n (%)	98 (61.2)	101 (63.9)	0.276
BMI (kg/m <sup>2</sup> )	32.8 $\pm$ 1.7	33.4 $\pm$ 1.4	0.551
Heart rate (bpm)	84 $\pm$ 12	85 $\pm$ 15	0.224
P-wave duration (ms)	114.6 $\pm$ 9.7	129.5 $\pm$ 8.3	<0.001
IAB, n (%)	45 (28.1)	102 (64.5)	<0.001
Hypertension, n (%)	98 (61.2)	107 (67.7)	0.036
Diabetes Mellitus, n (%)	91 (56.8)	97 (61.3)	0.092
Hyperlipidemia, n (%)	68 (42.5)	70 (44.3)	0.394
Smoking, n (%)	46 (28.7)	59 (37.3)	0.004
Systolic BP (mmHg)	129.4 $\pm$ 10.5	133.5 $\pm$ 10.3	0.106
Diastolic BP (mmHg)	79.2 $\pm$ 10.1	87 $\pm$ 10.6	0.001
Fasting Glucose (mg/dl)	121.5 $\pm$ 9.2	120.4 $\pm$ 10.4	0.509
Creatinine (mg/dl)	0.92 $\pm$ 0.3	0.91 $\pm$ 0.2	0.818
TC (mg/dl)	181.4 $\pm$ 30.3	205.2 $\pm$ 36.8	0.017
HDL-C (mg/dl)	41.3 $\pm$ 9.4	39.8 $\pm$ 10.2	0.366
LDL-C (mg/dl)	122.1 $\pm$ 38.5	129.6 $\pm$ 40.8	0.108
TG (mg/dl)	151.2 $\pm$ 43.4	155.4 $\pm$ 46.6	0.235
Hemoglobin (g/dL)	14.7 $\pm$ 1.3	14.5 $\pm$ 1.2	0.852
Platelet (K/uL)	286000 $\pm$ 115000	282000 $\pm$ 119000	0.404

Linear regression analysis was used to determine the independent predictors of the ascending aortic diameter. P-wave duration ( $\beta = 0.695$ ,  $p < 0.001$ ) and LAVI ( $\beta = 0.611$ ,

$p = 0.005$ ) were found to be independent predictors of ascending aortic diameter (Table 4).

**Table 2.** Transthoracic echocardiographic results of study population

	AAD group (-) (n = 160)	AAD group (+) (n = 158)	P value
LVEF (%)	61.7 ± 4.6	60.5 ± 4.4	0.517
Ascending aortic diameter (mm)	38.5 ± 4.2	43.4 ± 4.5	<0.001
Left atrium diameter (mm)	37.3 ± 4.7	40.5 ± 4.4	0.005
LAVI (ml/m <sup>2</sup> )	36.8 ± 16.9	41.7 ± 17.5	<0.001
LVSWT (mm)	9.7 ± 1.5	9.9 ± 1.8	0.186
PWT (mm)	8.6 ± 1.4	8.4 ± 1.4	0.248
LVEDD (mm)	48.5 ± 4.6	48.9 ± 4.8	0.475
LVEDS (mm)	32.6 ± 4.1	33.5 ± 4.2	0.613
E/A	1.22 ± 0.5	1.18 ± 0.4	0.335
Lateral e' (cm/s)	12.5 ± 3.5	11.4 ± 3.1	0.508
Septal e' (cm/s)	8.2 ± 1.5	8.7 ± 1.8	0.119
TAPSE (mm)	22.4 ± 3.8	23.2 ± 3.9	0.283

**Table 3.** The correlations of ascending aortic diameter with the study parameters

	Ascending aortic diameter	
	r	p
Age	0.485	0.008
BMI	0.274	0.044
Heart rate	0.121	0.386
P-wave duration	0.713	<0.001
Diastolic BP	0.542	0.001
Total cholesterol	0.105	0.537
Left atrium diameter	0.297	0.012
LAVI	0.604	<0.001

ROC curve analysis was used to determine the optimal cut-off value of P-wave duration for predicting the AAD. P-wave duration  $\geq 124$  msec. predicted AAD with a sensitivity of 88.3%, and specificity of 72.9%. (AUC: 0.818,  $p < 0.001$ , Figure 2).

## Discussion

In this study, we evaluated the association between AAD and IAB in obese patients. We demonstrated that prolongation of P-wave duration and increased LAVI values were significantly associated with ascending aortic diameter. We

think that this relationship is due to co-existing etiological factors and a common pathological process such as "oxidative stress" in the obesity rather than a causal relationship. To our knowledge, this is the first study evaluating the association between AAD and IAB in obese subjects.

**Table 4.** The independent association of the diameter of ascending aorta with study parameters

Independent variables	Dependent variable: Ascending aortic diameter					
	P	Beta (Standardized)	Beta $\pm$ SE (Unstandardized Coefficients)	P	Beta (Standardized)	Beta $\pm$ SE (Unstandardized Coefficients)
Age	0.273	0.348	0.09 $\pm$ 0.08			
BMI	0.305	0.117	0.32 $\pm$ 0.27			
Hypertension	0.436	0.095	0.75 $\pm$ 0.69			
Heart rate	0.394	0.158	0.35 $\pm$ 0.29			
P-wave duration	<.001	0.614	0.94 $\pm$ 0.15	<.001	0.695	1.05 $\pm$ 0.38
Diastolic BP	0.094	0.477	0.72 $\pm$ 0.19			
Total cholesterol	0.581	0.093	0.55 $\pm$ 0.32			
Smoking	0.119	0.388	0.37 $\pm$ 0.25			
Left atrium diameter	0.073	0.508	0.24 $\pm$ 0.06			
LAVI	0.026	0.575	0.18 $\pm$ 0.09	0.005	0.611	0.21 $\pm$ 0.08

Oxidative stress is defined as tissue damage occurring secondary to increased production and/or decreased destruction of reactive oxygen species (ROS). The nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase pathways are responsible for vascular oxidative stress (23). Beyond traditional risk factors for aortic aneurysms such as advanced age, HT and smoking; matrix metalloproteinases (MMPs) and ROS are also considered to be important risk factors in the pathophysiology of AAD (24). In a study published by Akkus et al. (2), native thiol and total thiol levels were demonstrated to be correlated with maximal aortic diameter. Total thiol level was also found to be an independent predictor of maximal aortic diameter in this study, and that thiol levels increased after surgical repair of the aorta. These results suggest that oxidative stress which increased in obesity is considered to

be involved in the AAD pathogenesis. Since the relationship between obesity and oxidative stress is well known, oxidative stress parameters were not evaluated in our study.

Obesity has complex effects on "cardiac" and "vascular" structures. Atrial tissue is important when we examine the "cardiac" effects of obesity. Obesity increases cardiac preload and alters atrial pressures, resulting in compensatory remodeling (25). Also, obesity directly drives electrophysiologic left atrial remodeling by finally leading to fibrosis of left atrium (26-28). Thus, we may consider IAB, which is the finding of atrial fibrosis process, as "cardiac atrial involvement" of obesity.

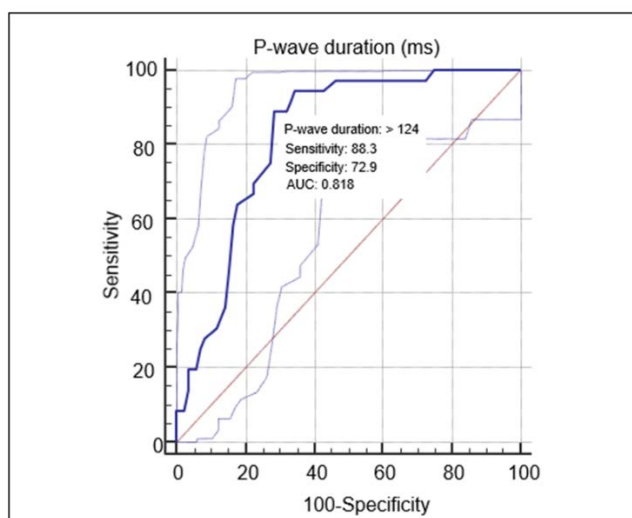


Figure 2. ROC curve of P-wave duration for predicting AAD

Ariyarajah et al. reported that IAB was associated with several pathophysiologic impairments that result in LA electro-mechanical dysfunction. They showed that the degree of conduction delay and IAB are directly correlated with LA enlargement (29). In addition, Dursun et al. (30) showed that P-wave duration and LA diameter significantly reduced after transcatheter aortic valve replacement indicating reverse atrial electrical remodeling. Similar to these studies, we also demonstrated that obese patients with AAD had significantly larger LAVI and increased P wave duration compared to patients without AAD. All these results suggest that LA diameter and LAVI has an important effect on P-wave duration.

In a study examining the relationship between obesity and IAB, Sun et al. aimed to determine the independent associations of obesity and HT with IAB. They found that systolic BP, diastolic BP and BMI were independently associated with P-wave duration (31). In accordance with this study, we also found that obese subjects with AAD had higher diastolic BP and higher frequency of IAB. In another study, Liu et al. assessed the effect of obesity on P-wave parameters (32). They measured maximum P-wave duration (Pmax), minimum P-wave duration (Pmin), and P-

wave dispersion (Pd) using a 12-lead electrocardiogram. They demonstrated that obesity was associated with increased Pmax and Pd, and increased prevalence of IAB. Also, they showed that the diameter of left atrium increased in the obese patients compared to control group. However, there is no information about the relationship among p-wave duration, LAVI and AAD in Liu et al.'s study. We found a significant association among these parameters in our study.

In a previous study which investigating the factors associated with AAD, Cetin et al. demonstrated that AAD was significantly associated with hair whitening and obesity (33). They thought that this relationship was not causal, which might exist mainly due to coexisting etiologic factors and parallel pathogenic processes. The findings of our study are also compatible with this study. We showed that BMI was positively correlated with ascending aortic diameter.

AAD is an important vascular disease and is associated with aortic dissection. Its clinical symptoms are not always sufficient for diagnosis and follow-up. Therefore, some electrocardiographic findings may be useful for diagnosis and follow-up of AAD. Our results suggest that P-wave duration may be used as a simple ECG finding in the follow-up of ascending aorta dilatation.

Our study had several limitations. First, the cross-sectional design of the present study precluded the demonstration of a causality relationship. Second, oxidative stress and inflammatory parameters were not evaluated in this study. Third, AAD was detected and quantified by TTE, and advanced imaging technique such as computed tomography imaging was not performed. Fourth, we didn't include normal weight people. Therefore, our results cannot be generalized to all patients with AAD. Future multicenter studies with larger participant are required to validate our findings. In conclusion, to our knowledge, this is the first study evaluating the association between AAD and IAB in obese subjects. We demonstrated that prolongation of P-wave duration and increased LAVI values were significantly associated with ascending aortic diameter. We proposed that P-wave duration may be used as a simple ECG finding in the follow-up of dilatation of the ascending aorta.

#### Ethics committee approval

Ethics committee approval was received from the Uşak University Training and Research Hospital for the study (Decision No: 152-05-23, Date: 7/1/2020).

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